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InheriGene

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Patient Details

Sample ID	2546325922_S1	**Sample Collection Date**	--/--/--
Sample Receiving Date	--/--/--	**Sample Reporting Date**	--/--/--
Patient Name	-	**Patient Location**	-
Age	-	**Gender**	-

Clinical Indications

DISEASE HISTORY		
PROBAND	**PARENTAL**	**SIBLING**
SELF	**FATHER** / **MOTHER**	
• **Global developmental delay, short stature, and facial dysmorphism. She has sparse hair, small wide-set eyes, a depressed nasal bridge, bilateral clinodactyly, a long second toe, Right eye estropia, intrauterine growth retardation observed in the USG scan, a Mongolian back spot, a tented upper lip and failure to thrive.**	- / -	

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Pathogenic variants detected related to the clinical phenotypes

Results:

Main Findings

Gene (Exon) [Transcript]	Variant (Amino acid Alteration)	Variant (Coding)	Inheritance	Zygosity	Disease	Interpretation
TBCK (exon15) [NM_001163435]	p.N457Tfs*15	c.1370delA	Autosomal Recessive	Homozygous	Hypotonia, infantile, with psychomotor retardation and characteristic facies 3 (OMIM: 616900)	Pathogenic
BTD (exon4) [NM_001370658]	p.D424H	c.G1270C	Autosomal Recessive	Heterozygous	Biotinidase deficiency (OMIM:253260)	Pathogenic

- Genetic test results are reported based on the recommendations of American College of Medical Genetics.
- There are Five-Tiered Classification based on ACMG guidelines [PMID: 25741868] i.e. Pathogenic, Likely Pathogenic, Variant of Unknown Significance (VUS), Likely Benign, Benign
- No other variant that warrants to be reported was detected. Variations with high minor allele frequencies which are likely to be benign will be given upon request.
- Data revaluation performed upon the upgradation of databases used and results may vary in accordance.

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Variant Interpretation

TBCK; c.1370delA; p.N457Tfs*15	
GENOMIC LOCATION	chr4:107156504
VARIANT TYPE	Frameshift
VARIANT ALLELE DEPTH	44
TOTAL ALLELE DEPTH	89
POPULATION FREQUENCY	gnomAD: .
ASSOCIATED DISEASE	Hypotonia, infantile, with psychomotor retardation and characteristic facies 3 (OMIM: 616900)
PREDICTION ALGORITHMS	SIFT: .; POLYPHEN: .; MUTATIONTASTER: . *D=DELETERIOUS/DAMAGING/DISEASE_CAUSING; T=TOLERATED; P=POSSIBLY DAMAGING; B: BENIGN; A: DISEASE-CAUSING AUTOMATIC; N: POLYMORPHISM; P: POLYMORPHISM_AUTOMATIC . = NO INFORMATION FOUND

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BTD; c.G1270C; p.D424H	
GENOMIC LOCATION	Chr3:15686693
VARIANT TYPE	Nonsynonymous
VARIANT ALLELE DEPTH	36
TOTAL ALLELE DEPTH	88
POPULATION FREQUENCY	gnomAD: 0.0285
ASSOCIATED DISEASE	Biotinidase deficiency (OMIM:253260)
PREDICTION ALGORITHMS	SIFT: D; POLYPHEN: D; MUTATION TASTER: A *D=DELETERIOUS/DAMAGING/DISEASE_CAUSING; T=TOLERATED; P=POSSIBLY DAMAGING; B: BENIGN; A: DISEASE-CAUSING AUTOMATIC; N: POLYMORPHISM; P: POLYMORPHISM_AUTOMATIC . = NO INFORMATION FOUND

Disease Summary

Hypotonia, infantile, with psychomotor retardation and characteristic facies 3

- A rare genetic disorder characterized by low muscle tone (hypotonia), developmental delay, intellectual disability, and distinctive facial features.
- The condition is usually diagnosed at birth or in early infancy and can lead to feeding difficulties, respiratory problems, and delayed motor milestones.
- The disease has a variable severity of symptoms and may be associated with other complications such as seizures and hearing loss.

Biotinidase deficiency

- Biotinidase deficiency is a rare genetic disorder caused by the inability to recycle biotin, a vitamin necessary for energy production and maintenance of healthy skin, hair, and mucous membranes.
- This condition leads to a buildup of biotin in the bloodstream, which eventually depletes due to impaired recycling mechanisms.
- Symptoms include neurological issues such as seizures, developmental delays, muscle weakness, and dermatitis.
- If left untreated, severe cases can lead to life-threatening complications, including coma or death. Early detection through newborn screening is crucial for effective management with biotin supplements.

Gene Summary

TBCK

- A variant with accession number VCV000225241 has been identified. This variant is titled 'NM_001163435.3(TBCK):c.1370del (p.Asn457fs)'. It is a Deletion variant, with a cDNA change of c.1370del and a protein change of N394fs, N418fs, N285fs, N457fs.The variant is located on chromosome 4, spanning from position 106235348 to 106235348.This variant is associated with the trait 'Hypotonia, infantile, with psychomotor retardation and characteristic facies 3' and has been classified as 'Pathogenic'.The review status for this variant is 'criteria provided, multiple submitters, no conflicts', and it was last evaluated on 2025/01/13 00:00.
- dbSNP link: https://www.ncbi.nlm.nih.gov/snp/746860249
- ClinGen link: https://reg.clinicalgenome.org/redmine/projects/registry/genboree_registry/by_caid?caid=CA358417
- TBCK, also known as TBC1 domain-containing kinase, plays a crucial role in regulating cellular processes such as endocytosis, exocytosis, and membrane trafficking. A pathogenic variant, NM_001163435.3(TBCK):c.1370del (p.Asn457fs), has been identified, leading to hypotonia, psychomotor retardation, and characteristic facial features in affected individuals. This deletion variant disrupts the protein's function, resulting in severe developmental delays and neurological impairments.

BTD

- A variant with accession number VCV000001900 has been identified. This variant is titled 'NM_001370658.1(BTD):c.1270G>C (p.Asp424His)'.It is a single nucleotide variant variant, with a cDNA change of c.1270G>C and a protein change of D424H.\nThe variant is located on chromosome 3, spanning from position 15645186 to 15645186.\nThis variant is associated with the trait 'not provided' and has been classified as 'Conflicting classifications of pathogenicity'.\nThe review status for this variant is 'criteria provided, conflicting classifications', and it was last evaluated on 2025/03/01 00:00.
- dbSNP link: https://www.ncbi.nlm.nih.gov/snp/13078881
- ClinGen link: https://reg.clinicalgenome.org/redmine/projects/registry/genboree_registry/by_caid?caid=CA090886
- The BTD gene plays a crucial role in the breakdown of certain amino acids, particularly phenylalanine. A variant, NM_001370658.1(BTD):c.1270G>C (p.Asp424His), has been identified on chromosome 3. This single nucleotide change may impact protein function, but its pathogenicity is disputed, with conflicting classifications.

Recommendations:

1. Genetic counseling is advised to interpret the potential consequences of the variant(s).
2. If results do not align with the clinical findings, additional testing should be considered based on the referring clinician's recommendation.
3. For confirmation of pathogenic variants, perform Sanger sequencing of the targeted region identified through preliminary screening, ensuring bidirectional sequencing for accuracy.

Methodology:

1. Sample Collection and Extraction, Library Preparation, and Sequencing was done by Partnered Lab.
2. Data Analysis:
   We use a customized algorithm developed at Genomiki Solutions for data analysis. The algorithm integrates quality control, read alignment to the human reference genome (GRCh38) using BWA, and variant identification tailored to enhance accuracy and efficiency for genomic data interpretation.
3. Clinical Annotation:
   Variants are annotated based on their clinical relevance using data from published literature and in-house curated databases. These curated databases provide key information, including minor allele frequency, to enhance the accuracy and depth of the annotation process.

Limitations:

1. Genetic testing may not always provide definitive answers due to evolving medical knowledge and technology.
2. Accurate interpretation relies on comprehensive clinical and family history. Misinterpretation may arise if such information is incomplete.
3. Variations in coding regions that cannot be sequenced due to technological constraints may not be identified.
4. Mosaicism, rare technical errors or recent transfusions may impact result accuracy.
5. The results are based on the available medical knowledge at the time of analysis; if new evidence arises, reanalysis can be requested.

Disclaimer:

1. Data Accuracy: The interpretations are based on the quality of the input data. Inaccurate or degraded sample quality may impact results.
2. Variant Classification: Variants classified as "Uncertain Significance" should not be used as the sole basis for clinical decisions. Further research or testing may be necessary.
3. Updates to Guidelines: As scientific understanding evolves; variant classifications and interpretations may change. Regular updates to clinical reports may be necessary.
4. Inheritance Patterns: This report does not account for inheritance patterns unless explicitly analyzed and reported.
5. Third-party Testing: Results from this report should not be compared with those from other laboratories without proper reconciliation of methodologies.
6. Scope of Testing: This test analyzes only the regions of interest specified. Variants outside the tested regions are not detected and cannot be interpreted.
7. Secondary Findings: This test does not analyze or report on unrelated secondary findings unless explicitly included in the test scope.
8. Laboratory Standards: All analyses are performed by current quality control and quality assurance standards relevant to the laboratory's accreditation.
9. Use of Computational Tools: Computational predictions provided (if any) are adjunctive to clinical judgment and are not definitive.
10. Counselling Recommendation: Patients are strongly encouraged to seek genetic counselling to understand the results and implications.
11. Non-diagnostic Nature: This test does not comprehensively assess all genetic disorders or conditions.
12. Data Sharing: Results and anonymized data may be used for quality control or research purposes, adhering to applicable data privacy regulations.

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